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ENVIRONMENTAL HEALTH PERSPECTIVES

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<http://dx.doi.org/10.1289/ehp.1205404>

Online 11 December 2012



NIEHS

National Institute of
Environmental Health Sciences

National Institutes of Health
U.S. Department of Health and Human Services

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Running title: Maternal Smoking and Childhood Obesity

Key words: animal, chemically induced/epidemiology, diabetes, environmental epidemiology, glucose, insulin, maternal smoking/*toxicity, metabolism, nicotine/*toxicity, obesity.

Acknowledgments: This review is based on deliberations that occurred at a January 11-13, 2011 workshop sponsored by the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP), U.S. Environmental Protection Agency (EPA), and the Food and Drug Administration National Center for Toxicological Research (FDA/NCTR) (<http://ntp.niehs.nih.gov/go/36433>). We gratefully acknowledge the contributions of Stephanie Holmgren (NIEHS) for developing the literature search strategy and Judy Stevens (GLP Support Services) and Kyla Taylor (NTP/NIEHS) for assistance in preparing the background literature review document. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the agencies that sponsored the workshop. We also acknowledge the invaluable assistance of the staff at the EPA National Center for Computation Toxicology (NCCT), in particular David Reif, David Dix, Keith Houck, and Richard Judson.

We would also like to thank Drs. Jerold Heindel and Matthew Longnecker, NIEHS for their excellent review of the manuscript.

The multidisciplinary workshop expert panel authored this article. Alison Holloway served as chair and Deepa Rao served as rapporteur for the Maternal Smoking/Nicotine workgroup. The following authors were also members of the workgroup: Mamta Behl, Kjersti Aagaard, Terry L. Davidson, Edward Levin, Theodore Slotkin, Supriya Srinivasan, David Wallinga and Morris White. Kristina Thayer was lead in assembling the literature review materials. Vickie Walker assisted with data extraction. Mamta Behl was lead author in preparing the workshop report.

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Funding and Conflict of interest

The authors declare they have no competing financial interests with respect to this manuscript, or its content, or subject matter. Mamta Behl is employed by Kelly Government Solutions, RTP, NC; Deepa Rao is employed by Integrated Laboratory Systems Inc., RTP, NC; David Wallinga is employed by Food and Health Program, Institute for Agriculture and Trade Policy, Minneapolis, MN.

Abbreviations

AGRP- Agouti related peptide

AMPK- Adenosine monophosphate activated protein kinase

AKT/PKB - protein kinase B

AUC- Area under the curve

BAT – brown adipose tissue

BMI - body mass index

BW - body weight

CART- Cocaine and amphetamine -regulated transcript

CI- confidence interval

dL - decilitre

eWAT - epididymal white adipose tissue

ERK1/2- Extracellular signal-regulated kinase

FKHR- Forkhead Homolog 1

GD - gestational day

GLUT4 - glucose transporter type 4

HFD- high fat diet

IGF-1- Insulin like growth factor -1

JAK2- Janus kinase 2

MAP2K1- Mitogen activated protein kinase 1

NPY- Neuropeptide Y

NTP - National Toxicology Program

OR - odds ratio

PAX6- Paired box gene 6

Pdx-1- Pancreatic and duodenal homobox 1

POMC-Proopiomelanocortin

PND - post natal day

sc - subcutaneous

SOCS3- Suppressor of cytokine signaling 3

STAT3- Signal transducer and activator of transcription 3

T1D - type 1 diabetes

T2D - type 2 diabetes

ABSTRACT

Background: An emerging literature suggests that environmental chemicals may play a role in the development of childhood obesity and metabolic disorders, especially when exposure occurs early in life.

Objective: Here we assess the association between these health outcomes and exposure to maternal smoking during pregnancy as part of a broader effort to develop a research agenda to better understand the role of environmental chemicals as potential risk factors for obesity and metabolic disorders.

Methods: PubMed was searched up to March 8, 2012 for epidemiological and experimental animal studies related to maternal smoking or nicotine exposure during pregnancy and childhood obesity or metabolic disorders at any age. A total of 101 studies, 83 in humans and 18 in animals, were identified as the primary literature.

Discussion: Current epidemiological data support a positive association between maternal smoking and increased risk of obesity or overweight in offspring. The data are strongly suggestive of a causal relation, however, the possibility that the association is due to unmeasured residual confounding cannot be completely ruled out. This conclusion is supported by findings from laboratory animals exposed to nicotine during development. The existing human literature does not provide support for an association between maternal smoking during pregnancy and type 1 diabetes in offspring. Too few human studies have assessed outcomes related to type 2 diabetes or metabolic syndrome to reach conclusions based on patterns of findings. There may be a number of mechanistic pathways important for the development of aberrant metabolic outcomes following perinatal exposure to cigarette smoke, which remain largely unexplored.

Conclusions: From a toxicological perspective, the linkages between maternal smoking during pregnancy and childhood overweight/obesity provide proof-of-concept of how early-life exposure to an environmental toxicant can be a risk factor for childhood obesity.

INTRODUCTION

Childhood obesity and diabetes are major threats to public health in the US and abroad. In the US, the prevalence of obesity among children and adolescents has almost tripled since 1980 with an estimated 16.9% of children and adolescents (i.e., approximately 12.5 million children and adolescents) considered obese (Ogden and Carroll 2010). This trend is also apparent in preschool children aged 2-5 years, where obesity was shown to increase from 5% in 1976-1980 to 10.4% in 2007-2008 (Ogden and Carroll 2010). Kim et al. (2006) reported an almost doubling in the prevalence of overweight in infants aged 0-6 months from 1980 to 2001 (3.4 to 5.9%) based on information from well-child visits at a large HMO in Massachusetts. Understanding the factors that contribute to the childhood obesity epidemic in order to identify intervention strategies is a critical public health need given that obesity is a known risk factor for diabetes and other chronic conditions such as heart disease (Reilly and Kelly 2011). Diabetes incidence, both type 1 and type 2, is also on the rise (2006; CDC 2011; Dahlquist et al. 2011; Patterson et al. 2009). Based on data from 2005-2008, 25.6 million, or 11.3%, of all people in the US aged ≥ 20 years have diagnosed or undiagnosed diabetes (CDC 2011). Although it is estimated that 70% of type 2 diabetes (T2D) can be attributed to being overweight or obese (Eyre et al. 2004), 30% of cases are not attributable to obesity. Therefore, factors other than changes in physical activity or diet may be contributing to this rise in childhood obesity and metabolic disorders. Indeed, there is growing concern that perinatal exposure to chemical insults may play a significant role in the increased incidence of obesity and metabolic disorders including diabetes, possibly through direct “diabetogenic” effects or by acting as “obesogens”.

Research addressing the role of environmental chemicals in childhood obesity and diabetes has rapidly expanded in the past several years. The May 2010 White House Task Force on Childhood Obesity (2010), the March 2011 NIH Strategic Plan for Obesity (2011), and the February 2011 Diabetes Strategic Plan from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK 2011) all acknowledge the growing science base in this area and cite the need to understand more about the role of environmental exposures as part of future research and prevention strategies. To help develop such a research strategy, the National Toxicology Program organized a state of the science workshop in January 2011 entitled “Role of Environmental Chemicals in the Development of Diabetes and Obesity.” (National Toxicology Program 2011). This review derives from discussions that occurred during that workshop.

IDENTIFICATION OF RELEVANT STUDIES

A PubMed search strategy updated until March 8, 2012 was developed to identify human and animal studies related to maternal smoking or tobacco exposure during pregnancy and (1) weight, growth, or adiposity after infancy (≥ 1 year of age in humans, after postnatal day 21 in rodents), or (2) health outcomes in offspring at any age related to type 1 or type 2 diabetes, glycemic control, or metabolic syndrome. Studies assessing growth in infants less than one year of age were excluded because maternal smoking during pregnancy is a known risk factor for low birth weight, whereas the primary question being addressed at the workshop was whether maternal smoking is a risk factor for childhood obesity. The literature search included both MeSH-based and a keyword strategies to identify articles not yet indexed in PubMed (see Supplemental Material for a complete list of search terms). This search identified a total of 1,551 publications (Supplemental Material, Figure S1). Of these, 99 studies presented original data that

met our inclusion criteria and were considered relevant as the primary literature. Two additional epidemiological studies identified during the peer-review process were also included (Fasting et al. 2009; Mendez et al. 2008) for a total of 101 studies (83 human studies and 18 animal studies).

MATERNAL SMOKING DURING PREGNANCY

Offspring Overweight or Obesity

Smoking during pregnancy is a known risk factor for low birth weight and small-for-gestational-age infants (Lumley et al. 2008; Oken et al. 2008; Samper et al. 2011), but is increasingly accepted as a risk factor for childhood overweight and obesity based on the consistent positive associations reported among studies (Figure 1). The majority of studies (34 of 42) summarized in Figure 1 present results that support a causal link between maternal smoking and subsequent child overweight or obesity. Many of these studies were evaluated in two recent meta-analyses (Ino 2010; Oken et al. 2008). Based on results reported in 14 observational studies, maternal smoking during pregnancy was associated with overweight at 3–33 years of age [pooled adjusted odds ratio (OR) 1.50; 95% CI: 1.36, 1.65] (Oken et al., 2008). The pooled OR estimated by Ino (2010) for obesity (BMI > 95th percentile) was 1.64 (95% CI: 1.42, 1.90) based on 16 studies. Women who smoked during pregnancy tended weigh more, and tended to have lower social/economic status, less education, and were less likely to breastfeed (Ino 2010; Oken et al. 2008). Both meta-analyses used funnel plot methods to ascertain publication bias and concluded there was some evidence for publication bias, but not enough to negate the overall conclusion of increased risk.

Ethnicity may affect the association between maternal smoking and childhood obesity. A large retrospective study by Sharma et al. (2008) of the PedNSS cohort found significant associations between maternal smoking and childhood obesity only in white ($n=66,191$) and black ($n=28,230$) children; the associations were not apparent for Hispanic ($n=34,378$), American Indian/Alaska national ($n=2,228$), or Asia/Pacific children ($n=4,740$). The lack of association in children of Asian/Pacific Island descent is interesting since studies on Japanese children have reported findings consistent with a positive relationship (Ino et al. 2011; Mizutani et al. 2007; Suzuki et al. 2009; Suzuki et al. 2010). Too few studies are available on Native American and Hispanic children to interpret the findings of Sharma et al. (2008) in the context of other studies. One Brazilian study by Tome et al. (2007) did not find an association between maternal smoking and offspring overweight at 8 to 10 years of age (adjOR = 1.07; 95% CI: 0.84-1.37); however, they did find that children of mothers who smoked were less likely to be underweight (adjOR = 0.56; 95% CI: 0.40-0.78). It is worth noting that this study was conducted in the Ribeirao region of Brazil where 9.5% of the children were malnourished ($\text{BMI} < 5^{\text{th}}$ percentile).

Unmeasured confounding

While the literature on the association between maternal smoking and obesity/overweight in offspring is fairly consistent when looking across studies, there are some indications that unmeasured familial or lifestyle factors may contribute to the association. One study conducted sibling-based analyses to evaluate the relationship between maternal smoking and BMI in 124,203 males born between 1983-1988 identified in the Swedish Medical Birth Registry with the intent of investigating the impact of familial factors on the association between maternal smoking and offspring obesity (Iliadou et al. 2010). They reported an association between maternal smoking during the first trimester and overweight ($\text{BMI} \geq 25$) for the cohort as a whole

(adjusted odds ratio = 1.56; 95% CI: 1.46, 1.66 for >10 cigarettes per day compared to 0 cigarettes). However, the authors found smaller associations based on within-family analyses, suggesting partial confounding by familial factors. Gilman et al. (2008) also conducted a sibling-based analysis of children enrolled in the Collaborative Perinatal Project to address the issue of unmeasured confounding factors by fitting conditional fixed-effect models among siblings. This type of analysis capitalizes on variability in exposure to tobacco smoke that can occur among siblings when the mother's smoking pattern during gestation differed across pregnancies. Conceptually, the sibling analysis matches exposed and unexposed siblings on family background to identify evidence of unmeasured sources of confounding. Gilman et al. (2008) found significant positive associations in the full cohort for overweight at age 7 were still apparent in the conditional sibling fixed effects analysis.

Second hand smoke exposure during pregnancy or childhood

Although the literature search strategy and inclusion criteria were constructed to identify studies assessing maternal smoking during pregnancy, several studies of paternal or "partner" smoking during pregnancy (Durmus et al. 2011b; Kwok et al. 2010; Leary et al. 2006; Matijasevich et al. 2011) or during childhood (von Kries et al. 2008) were identified. Some of these studies reported no association between parental/partner smoking and BMI or adiposity endpoints (Durmus et al. 2011b; Matijasevich et al. 2011) while others did (Kwok et al. 2010; Leary et al. 2006; von Kries et al. 2008) suggesting that paternal/partner smoking may be a contributing factor on its own, either by unmeasured familial factors, or as a contributor to maternal exposure from second hand smoke. Another study by Steur et al. (2010) assessed predictors of obesity at 8 years of age in 1,687 children participating in the Prevention and Incidence of Asthma and Mite Allergy

(PIAMA) study, a prospective study based in the Netherlands. Maternal smoking during pregnancy and “smoking in the parental house” were both included in the model selection, but only “smoking in the parental house” was selected as a significant independent predictor of childhood overweight.

Other Measures of Adiposity, BMI, and Leptin

The findings discussed above focus on studies of associations between maternal smoking and overweight or obesity. Other studies have estimated associations between maternal smoking during pregnancy and continuous measures of BMI, standardized BMI (i.e., z-score or standard deviation score), or body weight in the offspring (see Supplemental Material, Table S1) (Beyerlein et al. 2011; Beyerlein et al. 2010; Durmus et al. 2011a; Goldani et al. 2007; Hill et al. 2005; Iliadou et al. 2010; Kannelopoulos et al. 2007; Leary et al. 2006; Matijasevich et al. 2011; Ravnborg et al. 2011; Suzuki et al. 2010; Syme et al. 2010). Overall, these studies have reported positive associations with maternal smoking during pregnancy and offspring BMI. There are also indications that the children of mothers who smoked during pregnancy display more rapid weight gain earlier in life (Griffiths et al. 2010; Karaolis-Danckert et al. 2008; Wen et al. 2011).

Studies in the literature often assess obesity based on BMI, which is not necessarily a direct measure of adiposity since it does not distinguish fat and lean mass (Freedman and Sherry 2009; Wells 2001). Associations between maternal smoking and indicators of adiposity (i.e., body fat, abdominal fat, skin fold thickness) [Supplemental Material, Table S2 (Durmus et al. 2011a; Leary et al. 2006; Silva et al. 2010; Syme et al. 2010; Vik et al. 1996; von Schnurbein et al. 2011)] are less consistent than associations with overweight/obesity or continuous measures of

BMI-related endpoints (Figure 1). Given the limitations of BMI as a measure of adiposity, it is therefore important for future studies to consider other more direct measures of adiposity/fat mass to clarify the contribution of maternal smoking to childhood obesity.

Leptin, a protein produced by adipocytes and placental tissue, appears to function as a link between adiposity, satiety, and energy regulation (Lee and Fried 2009; Pelleymounter et al. 1995; Woods and D'Alessio 2008). Leptin levels have been correlated with neonatal growth (Christou et al. 2001; Vatten et al. 2002), but very few studies have looked at leptin levels beyond the neonatal period, and it is unclear how informative the infant studies are for addressing issues related to childhood obesity given the complex role that maternal smoking has on childhood growth (i.e., as a risk factor for low birth weight and for childhood obesity). Overall, the findings on leptin levels in cord blood or blood collected from infants in association with maternal smoking status are mixed, with some studies reporting positive associations (Helland et al. 2001), negative associations (Mantzoros et al. 1997; Ozkan et al. 2005), or no association (Coutant et al. 2001; Kayemba-Kay's et al. 2008; Pardo et al. 2004; Vatten et al. 2002).

Type 1 Diabetes

The existing human studies do not provide support for an association between maternal or parental smoking during pregnancy and childhood type 1 diabetes (T1D) (Figure 2). Only 2 of the 13 studies assessing endpoints related to T1D following exposure during pregnancy reported findings consistent with an association (Sipetic et al. 2005; Wahlberg et al. 2011). In Sipetic et al. (2005) the frequency of maternal smoking during pregnancy was higher in T1D cases

compared to controls (37.2% versus 24.8%, $p = 0.023$ or unadjusted OR = 1.79; 95%CI: 1.08, 2.97). Although the univariate finding was statistically significant, the authors did not include maternal smoking in the multivariate analysis conducted to identify risk factors for T1D. In Wahlberg et al.(2011), a positive association was observed for one indicator of beta cell autoimmunity in T1D, tyrosine phosphatase (IA-2A)+ antibody status (unadjusted OR = 1.6; 95%CI: 1.2, 2.2), and not for glutamic acid decarboxylase (GAD)+ antibody status (data not shown). None of the five prospective studies reported a positive association between maternal or paternal smoking during pregnancy and T1D (Hummel et al. 2001; Johansson et al. 2008; Rosenbauer et al. 2007; Stene et al. 2004; Toschke et al. 2007a; Wadsworth et al. 1997) including two studies of children who were considered at high risk for developing the disease (Hummel et al. 2001; Stene et al. 2004). Several studies reported that T1D was less likely among children whose mothers smoked during pregnancy than among the children of nonsmoking mothers (Dahlquist and Kallen 1992; Marshall et al. 2004; Svensson et al. 2005) for T1D. A study by Hummel et al. (2001)reported a non-significant negative association between islet cell antibodies (a marker of beta cell autoimmunity) and maternal smoking during pregnancy among children considered at high risk because one or both parents had T1D. However, the number of cases in this study was small (47/1,043 children). One hypothesis suggested to explain evidence of a protective effect of exposure to smoking relates to the hygiene theory of autoimmune disease, which suggests that the risk of autoimmune disease may be increased if the environment is “cleaner,” which might be manifest in the households of non-smokers (Johansson et al. 2008; Marshall et al. 2004). Alternatively, smoking may affect immune function, resulting in a reduced risk of developing autoimmune disorder (Prescott 2008).

Although the overall literature does not support an association between maternal smoking during pregnancy and T1D in offspring, associations with exposure to smoke during childhood should be investigated further. Two studies have assessed childhood exposure and T1D, and both reported findings supportive of an association (Hathout et al. 2006; Sipetic et al. 2005; Skrodeniene et al. 2008). In Skrodeniene et al. (2008) Lithuanian children who were islet cell autoantibody positive were more likely to live in a home where family members smoked indoors than children who were islet cell autoantibody negative [7 of 13 (53.8%) versus 53 of 199 (26.6%), respectively, $p = 0.004$; unadjusted OR = 3.21; 95%CI: 1.03, 10.00]. The frequency of mothers who reported smoking during pregnancy did not differ between the groups in this study. Hathout et al. (2006) reported that children with T1D were more likely to have been exposed to passive smoking than control children in Southern California [31 of 102 cases (30%) versus 3 of 10 controls (10%), $p = 0.0001$; unadjusted OR = 3.90; 95%CI: 1.19, 17.24]. One limitation in the existing literature that needs to be addressed in future studies investigating the association of smoking or other environmental exposures and T1D is use of statistical models that consider potential confounding factors, e.g., viruses, nutrition, or socioeconomic psychosocial factors.

Type 2 Diabetes and Metabolic Syndrome

Fewer studies have looked at associations between maternal smoking during pregnancy and type 2 diabetes (T2D), blood glucose, blood insulin or metabolic disease (Horta et al. 2011; Huang et al. 2007; Montgomery and Ekblom 2002; Thiering et al. 2011a; Thomas et al. 2007)(Figure 3). It is not possible to reach conclusions with confidence based on the existing literature because of the variation in health outcomes assessed among the studies, i.e., HbA1C; fasting glucose, non-fasting glucose, HOMA-IR, blood insulin; T2D; and metabolic syndrome. In addition, although

most of the studies do not report positive associations with these outcomes, the age at assessment in many of the studies was relatively young and additional follow-up may be required. It is worth noting that no association with $\text{HbA1C} \geq 6\%$ was found in the oldest and largest cohort assessed [7,518 men and women from the 1958 British birth cohort enrolled in the Perinatal Mortality Survey (PMS) evaluated at 45 years of age] (Thomas et al. 2007). This finding does not confirm an earlier report for the same cohort of an association between heavy smoking during pregnancy and T2D in offspring at 33 years of age (adjusted OR = 4.02; 95% CI: 1.14, 14.14) (Montgomery and Ekbom 2002). A related analysis of the cohort by Power et al. (2010) also reported no association with HbA1C in adults at age 45 years [fully adjusted mean difference = 0.13; 95% CI: -0.33, 0.58]. Power et al. (2010) reported a positive association between maternal smoking during pregnancy and metabolic syndrome based on an unadjusted model [unadjusted OR = 1.21; 95% CI: 1.05, 1.39], but there was a significant negative association between maternal smoking and metabolic syndrome after adjustment for adult life covariates such as social class, education, physical activity and inactivity (television/computer use), smoking, and consumption of fruit/vegetables, cakes/sweets and alcohol (adjusted OR = 0.55; 95% CI: 0.47, 0.64).

ANIMAL STUDIES ON DEVELOPMENTAL EXPOSURE TO NICOTINE

There are 599 known cigarette additives (Rabinoff et al. 2007) and most are uncharacterized for potential toxicity, including metabolic effects. One exception is cadmium, a constituent of tobacco of smoke shown to alter glucose homeostasis or insulin sensitivity in animals exposed as adults (Edwards and Prozialeck 2009) but have not been assessed for metabolic effects after developmental exposure. Only two studies assessed prenatal exposure to cigarette smoke during pregnancy and body weight later in life in offspring (Chen et al. 2011; Ng et al. 2009).

Body weight and adiposity

Most animal studies have reported that rats exposed to nicotine during perinatal development tended to have a higher body weight and more fat mass compared to controls (Figure 4) with the effect typically first apparent at weaning and persisting through adulthood (Gao et al. 2005; Newman et al. 1999; Oliveira et al. 2009; Oliveira et al. 2010a; Somm et al. 2008). However, there are exceptions to this pattern (Gao et al. 2008; Holloway et al. 2007), which do not appear to be attributable to strain differences, dosing or the timing of exposure. Food intake was unaffected in studies that evaluated it as an end-point (Oliveira et al. 2009; Oliveira et al. 2010a; Somm et al. 2008). The potential interaction between perinatal nicotine exposure and postnatal diet has only been explored in one study, which examined whether a high fat diet (HFD) postnatally would exacerbate the weight gain in nicotine-exposed animals (Somm et al. 2008). Although the nicotine-treated animals that were fed a HFD did not consume more kcal than controls fed the same diet, they were heavier. The nicotine-treated animals were less physically active than control animals consuming the same diet. There were no differences in oxygen consumption or respiratory exchange ratio, suggesting that increased weight gain in HFD animals with the same caloric intake were perhaps due to the dysregulation of adipose tissue development thereby leading to higher amounts of fat storage.

Glucose homeostasis and insulin sensitivity

There are several reports in the literature on impaired glucose homeostasis in the male offspring of rats that were treated with nicotine during gestation (Somm et al. 2008), lactation (Oliveira et al. 2010a), or gestation and lactation (Bruin et al. 2007; Bruin et al. 2008c; Holloway et al. 2005)(Figure 5). Administered doses ranged from 1 to 6 mg/kg-day delivered to the mother

either via an osmotic mini-pump implanted under the skin or via daily subcutaneous injections. These dosing protocols resulted in maternal serum cotinine levels considered relevant to women who smoke or use nicotine patches as cigarette substitutes (Bruin et al. 2007; Hackman et al. 1999; Somm et al. 2009). The most consistent findings from these studies were indications of insulin resistance in adulthood based on increased insulin area under the curve (AUC) following an oral or intraperitoneal glucose challenge (Bruin et al. 2007; Bruin et al. 2008c; Holloway et al. 2005; Somm et al. 2008) or on an increased insulin resistance index (Oliveira et al. 2010a). These effects were seen across studies despite the use of different doses of nicotine, different administration protocols, and different windows of developmental exposure within the perinatal period (i.e., gestation and/or lactation). A study by Holloway et al. (2007), reported increased insulin resistance in 15-week old F2 generation male offspring of dams that were treated with nicotine only during gestation and lactation compared with untreated controls. Impairments in glucose tolerance also have been reported following nicotine exposure (Bruin et al. 2007; Bruin et al. 2008c; Holloway et al. 2005; Somm et al. 2008). Effects on fasting insulin levels have been less consistent, with some studies showing no effect (Bruin et al. 2007; Somm et al. 2008) and others reporting increased levels in adult rodents compared to untreated controls (Holloway et al. 2007; Holloway et al. 2005; Oliveira et al. 2010a). At low dose levels (1 mg/kg-d) permanent changes in glucose homeostasis were observed only when exposure occurred during both fetal and neonatal life (i.e., pregnancy and lactation), however when dams were exposed to 3mg/kg-d (Somm et al. 2008) or 6mg/kg-d (Oliveira et al. 2010a), then either fetal or lactational exposure was sufficient to affect glycemic control. Importantly, no effects on glucose homeostasis were observed in Wistar rats (Jose et al. 2009) or in a series of studies in Sprague-Dawley rats (Jose et al. 2009; Swislocki 2003; Swislocki and Fakiri 2008; Swislocki et al. 1997) treated with nicotine

after weaning. Taken together, these data suggest that cigarette smoke or nicotine exposure during gestation and lactation is the critical window of exposure.

Pancreatic effects

Changes in pancreatic weight, morphology and function have been reported in animals that were treated with nicotine during gestation alone or during gestation and lactation (Bruin et al. 2008a; Bruin et al. 2007; Bruin et al. 2008b; Grove et al. 2001; Holloway et al. 2005; Somm et al. 2008)(Figure 6). These pancreatic effects include increased β -cell apoptosis and decreased β -cell mass in rodents (Bruin et al. 2007; Holloway et al. 2005; Somm et al. 2009). Other findings include decreased pancreatic weight in infant Rhesus monkeys (Grove et al. 2001). As noted earlier, the treatment protocols used in the rodent studies result in maternal serum cotinine levels that are considered relevant to women who smoke or use nicotine patches as cigarette substitutes. The pancreatic effects are hypothesized to occur as a direct effect of nicotine binding to nicotinic acetylcholine receptors in the developing pancreas, leading to oxidative stress and mitochondrial damage and eventual β -cell apoptosis (Bruin et al. 2008a; Bruin et al. 2007; Bruin et al. 2008b; Bruin et al. 2008c). Pancreatic tissue is considered to be especially susceptible to oxidative-stress mediated tissue damage due to low levels of antioxidant enzyme expression (Lenzen et al. 1996; Tiedge et al. 1997).

Leptin signaling

Adipose tissue is increasingly recognized as an active endocrine organ with many secretory products. In addition, adipose tissue is considered to be part of the innate immune system(Gaspari et al. 2011). Leptin is one of the key hormones involved in feeding behavior and

energy expenditure [reviewed in Belgardt et al. (2010)]. In general terms, leptin is secreted from the adipocytes of white adipose tissue and delivers information on peripheral energy stores to the central nervous system. Leptin resistance that involves impairment in leptin transport, leptin signaling, and/or the neuro-circuitry of energy balance is a risk factor for obesity (Morris and Rui 2009). Several studies have assessed leptin levels or the expression of proteins involved in leptin signaling following developmental nicotine exposure (Grove et al. 2001; Huang and Winzer-Serhan 2007; Santos-Silva et al. 2010). Findings from animal studies reveal that early exposure to nicotine appears to be associated with dysregulation of leptin levels, likely via hypertrophy of adipocytes and increased gene expression of pro-adipogenic transcription factors (Somm et al., 2008), and hypothalamic leptin signaling (Oliveira et al. 2009; Oliveira et al. 2010a).

The association between smoking and leptin levels in human infants remains controversial, with both hyper- and hypo-leptinemia being reported (Coutant et al. 2001; Helland et al. 2001; Kayemba-Kay's et al. 2008; Mantzoros et al. 1997; Ozkan et al. 2005; Pardo et al. 2004; Pardo et al. 2005; Vatten et al. 2002).

CONCLUSIONS AND RESEARCH RECOMMENDATIONS

In conclusion, based on human epidemiological studies and animal experiments reported in the literature, current evidence supports a causal relationship between maternal smoking and increased risk of obesity or overweight in offspring; however, the possibility that the association is due to unmeasured residual confounding cannot be completely ruled out. The literature is not sufficient to evaluate the potential impact of maternal smoking after delivery, or the contribution of exposure to second hand smoke during pregnancy and early childhood. Existing studies in humans do not provide strong support for an association between maternal or parental smoking

and childhood T1D, and too few epidemiological studies have assessed outcomes related to T2D to reach conclusions. However, findings from animal studies identify associations between perinatal nicotine exposure and disruption of pathways important in the pathophysiology of type 2 diabetes, including reduced beta cell mass and impaired beta cell function.

In Appendix 1 we identify research gaps and provide specific study recommendations noting in particular the need to better understand the (1) relationship between developmental exposure to tobacco smoke as a risk factor for T2D or metabolic syndrome, (2) consequences of pre- and post-natal exposure to second hand smoke (SHS; also called environmental tobacco smoke, involuntary smoke, and passive smoke), (3) impact of timing of exposure, dose, duration and route (e.g., nicotine replacement therapy), and (4) the mechanistic basis for the association between cigarette smoke or nicotine exposure with childhood obesity and metabolic outcomes. Elucidating the mechanistic basis for these associations could be an important component of developing a toxicological screening approach that could be used to identify other environmental chemicals for targeted assessment of obesogenic and metabolic effects. For example, a number of pesticides included in Phase 1 of EPA's ToxCast™ high throughput screening program(EPA)interact with nicotinic receptors but have never been assessed for potential adipogenic or metabolic effects (Supplemental Material, Figure S2). Addressing the data gaps can help us understand more about the nature of the association as well as inform decisions regarding intervention strategies. Epidemiological studies will also need to consider the challenges related to validity of self-reported maternal tobacco use or SHS exposure, especially in studies evaluating the long-term health consequences for offspring where exposure assessment may occur many years after the exposure event. With respect to mechanistic research, more

attention should be given to the possibility that environmental exposures could alter central nervous system (CNS) regulation of energy and body weight homeostasis. The brain is the primary organ involved with determining behavior and obesity; metabolic diseases are often considered to be manifestations of behavioral excess (i.e., consuming calories in excess of one's energy needs). There are a number of pathways important for the development of obesity and/or diabetes, including but not limited to: alterations in neurohumoral signaling, feeding behavior, energy balance, brain and peripheral inflammation and insulin resistance. To date, the effects of maternal cigarette smoking and/or nicotine exposure on these pathways remains largely unexplored (Wilborn et al. 2005; Woods 2009; Woods and D'Alessio 2008; Zheng et al. 2009). Another largely unexplored hypothesis is that fetal/neonatal exposure to smoking/nicotine sensitizes the offspring to adverse effects of obesogenic diets. Although perturbations in the microbiome profile have been associated with diabetes and obesity, the contribution/interactions with smoking have not been explored and may also influence susceptibility to adverse diets.

The association between maternal smoking and childhood obesity add to the recognized health burden from tobacco exposure, which is estimated at almost 5 million deaths per year globally (WHO 2010). Maternal smoking during pregnancy may not account for as many cases of childhood obesity or overweight as more traditional risk factors such as decreased physical activity, watching television >1 h/day, and low parental education level (Toschke et al. 2007b), but it is a risk factor that, if prevented, can help reduce the burden of childhood obesity at the population level. From a toxicological perspective, the linkages between maternal smoking during pregnancy and childhood overweight/obesity provide proof-of-concept of how early-life exposure to an environmental toxicant can act as a risk factor for childhood obesity.

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Appendix 1. Data Gaps and Research Needs.

Epidemiology

- Additional assessment of association between maternal smoking and risk of T2D and metabolic syndrome in offspring
 - Clarification of the pre- and post-natal consequences of SHS on childhood obesity and metabolic outcomes
 - Characterization of factors such as timing of exposure (including adolescence), dose, duration and route (e.g., nicotine replacement therapy)
 - Evaluate potential confounding by or interactions with postnatal diet and activity levels
 - Consider studies of nicotine replacement therapy (NRT) to better establish the association between nicotine and obesity or diabetes and other metabolic disorders in humans
 - NRT during pregnancy trials, NRT following smoking cessation, nicotine therapeutics for non-smokers, Snus (a moist powder tobacco product similar to dry snuff)
 - Other data may be available from FDA for nicotinic acetylcholine receptor agonist drugs, and putative “reduced” harm cigarettes
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Animal and In Vitro

- Better understanding of the basic biology of critical cells (i.e. adipocytes, beta-cells) and their function in health and disease, including how the biology that controls body weight and metabolic set points change with life stage
 - Further characterize impact of factors such as timing of exposure, dose, duration and route (e.g., nicotine replacement therapy) on adiposity, diabetes, and metabolic-related health outcomes
 - Mechanistic effects of smoking on genomic/epigenomic and molecular targets that coordinate central and peripheral nutrient homeostasis and metabolic function.
 - Determine the relative contribution of other constituents of cigarette smoke.
 - Graded step wise manner—starting with high throughput-type screening with relevant cell types, then *in vivo alone* and then *in vivo* in combination with nicotine.
 - Evaluate interactions between fetal/neonatal exposure to smoking/nicotine and postnatal diet and activity levels
 - Assess the effects of other chemicals that act as agonists for nicotinic acetylcholine receptors (nAChRs), such as neo-nicotinoid pesticides as well as chemicals identified in EPA’s ToxCast™ high throughput screening program (Supplemental Material Figure 2)
-

SHS = second hand smoke, also called environmental tobacco smoke, involuntary smoke, and passive smoke

FIGURE LEGENDS

Figure 1. Human studies on maternal smoking during pregnancy and childhood overweight and obesityError! Reference source not found.

Sort Order: The primary grouping of studies is based on study design (cross-sectional, prospective, or retrospective). Within each study design, main findings are grouped by whether the outcome was overweight (red) or obesity (black). Studies are then sorted alphabetically within these grouping categories.

Abbreviations: Amer. Ind = American Indian; ALSPAC = Avon Longitudinal Study of Parents and Children; adjOR = adjusted odds ratio; AMICS = Asthma Multicenter Infant Cohort Study; BBC = British Birth Cohort; BMI = body mass index; CESAR = Central European Study on Air Pollution and Respiratory Health; CLASS = Children's Lifestyle and School Performance study; CPP = Collaborative Perinatal Project; GDM = gestational diabetes mellitus; Gen R = Generation R study; NCDS = National Child Development Study; NLSY = National Longitudinal Survey of Youth; PACT = Prevention of Allergy among Children of Trondheim study; PedNSS = Pediatric Nutrition Surveillance System; PrevOR = prevalence ratio; WIC = Women, Infants, and Children program; RR= relative risk; wt. = weight; ref. = referent group

*Relative risk estimates for bracketed statistics, i.e., [crudeRR] calculated based on data presented in the paper using an open source epidemiology statistics programs, OpenEpi (<http://www.openepi.com/menu/openEpiMenu.htm>)

Figure 2. Human studies on exposure to smoking during pregnancy related to T1D

Sort Order: Studies are grouped by the nature of the smoke exposure (maternal, paternal, or second hand smoke during childhood). Studies are then sorted by specific outcome measure (e.g., GAD Ab+), and presented alphabetically within a given outcome measure.

Abbreviations: adjOR = adjusted odds ratio; ABIS = All Babies in Southeast Sweden cohort; autoAb = auto antibodies; BBC = British Birth Cohort; BCS70 = 1970 British Birth Cohort study; BPASU = British Paediatric Association Surveillance Unit; CC = case control; cross-sect. = cross-sectional; DAISY = Diabetes Autoimmunity Study in the Young; ESPED = German pediatric surveillance unit; GADA = glutamic acid decarboxylase antibodies; IA-2A = insulinoma antigen 2A; NCDS = National Child Development Study; OR = odds ratio; pros. = prospective; retro. = retrospective; RR = relative risk; T1D = type 1 diabetes* Relative risk estimates for bracketed statistics, i.e., [crudeRR] calculated based on data presented in the paper using an open source epidemiology statistics programs, OpenEpi (<http://www.openepi.com/menu/openEpiMenu.htm>)

Figure 3. Human studies on exposure to smoking during pregnancy and findings related to T2D or metabolic syndrome

Sort Order: The primary grouping is whether the outcome was related to T2D, glucose, or insulin (black), or metabolic syndrome (blue). Studies are then sorted by specific outcome measure (e.g., HOMA-IR) and presented alphabetically within a given outcome measure.

Abbreviations: A1C = glycosylated haemoglobin A1c; adjMR = adjusted mean ratio; adjOR = adjusted odds ratio; BBC = British Birth Cohort; cross-sect. = cross-sectional; GINIplus = German Infant Nutritional Intervention study; HOMA-IR = Homeostatic model assessment for

insulin resistance; LISApplus = Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood study; NCDS = National Child Development Study; OR = odds ratio; pros. = prospective

Figure 4. Animal studies of prenatal or prenatal to lactational exposure to nicotine or cigarette smoking and adiposity-related endpoints Error! Reference source not found.

Sort Order: The primary grouping of studies is based on whether the endpoint was related to adiposity or body weight. Within each endpoint category, main findings are grouped by whether the exposure was to nicotine or cigarette smoke. Within each exposure category, main findings were sorted based on specific endpoint (A to Z).

Abbreviations: AUC = area under the curve; BAT = brown adipose tissue; BW = body weight; eWAT = epididymal white adipose tissue; GD = gestational day; inhal = inhalation; inj = injection; MCS = mainstream cigarette smoke; PND = postnatal day; sc = subcutaneous; w = weeks

[] Value was assumed or estimated based on data presented in publication

*Statistically significant effect at specified dose level as reported in publication

◇ In some cases statistical significance of percent control response differs from author's interpretation, e.g., author's statistical analysis considered multiple comparisons, i.e., ANOVA

Δ Dose level summarized in graph

‡ In Ng et al. (2009) animals were exposed via whole body inhalation to mainstream cigarette smoke (smoke inhaled by an active smoker) at a particle concentration of 15 mg/m³; In Santos-Silva et al. (2011) animals received smoke generated from an automatic cigarette-smoking machine that generated a smoke mixture containing 89% sidestream smoke (smoke released from the burning end of a cigarette) and 11% mainstream smoke as a surrogate for active

smoking. In Chen et al. (2011) dams were exposed to cigarette smoke via a perspex chamber for 30 minutes 5 days a week (2 cigarettes/day, nicotine \leq 1.2 mg, carbon monoxide \leq 15 mg).

Figure 5. Animal studies of prenatal or prenatal to lactational exposure to nicotine and glucose homeostasis-related endpoints

Sort Order: The primary grouping of studies is based on whether the endpoint was based on glucose or insulin. Within the endpoint category, main findings were sorted based on specific endpoint (A to Z).

Abbreviations: AUC = area under the curve; h = hours; ipGTT = intraperitoneal glucose tolerance test; inj = injection; OGTT = oral glucose tolerance test; PND = postnatal day; sc = subcutaneous; w = weeks

[] Value was assumed or estimated based on data presented in publication

*Statistically significant effect at specified dose level as reported in publication

◇ In some cases statistical significance of percent control response differs from author's interpretation, e.g., author's statistical analysis considered multiple comparisons, i.e., ANOVA

Figure 6. Animal studies of prenatal or prenatal to lactational exposure to nicotine and pancreatic endpoints

Sort Order: The primary grouping of studies is based on the type of pancreatic effect. Within the effect category, main findings were sorted based on whether treatment occurred only during prenatally (black) or prenatal + lactational (green)

Abbreviations: sc = subcutaneous; w = weeks

[] Value was assumed or estimated based on data presented in publication

*Statistically significant effect at specified dose level as reported in publication

Figure 1. Human studies on maternal smoking during pregnancy and risk for childhood overweight and obesity

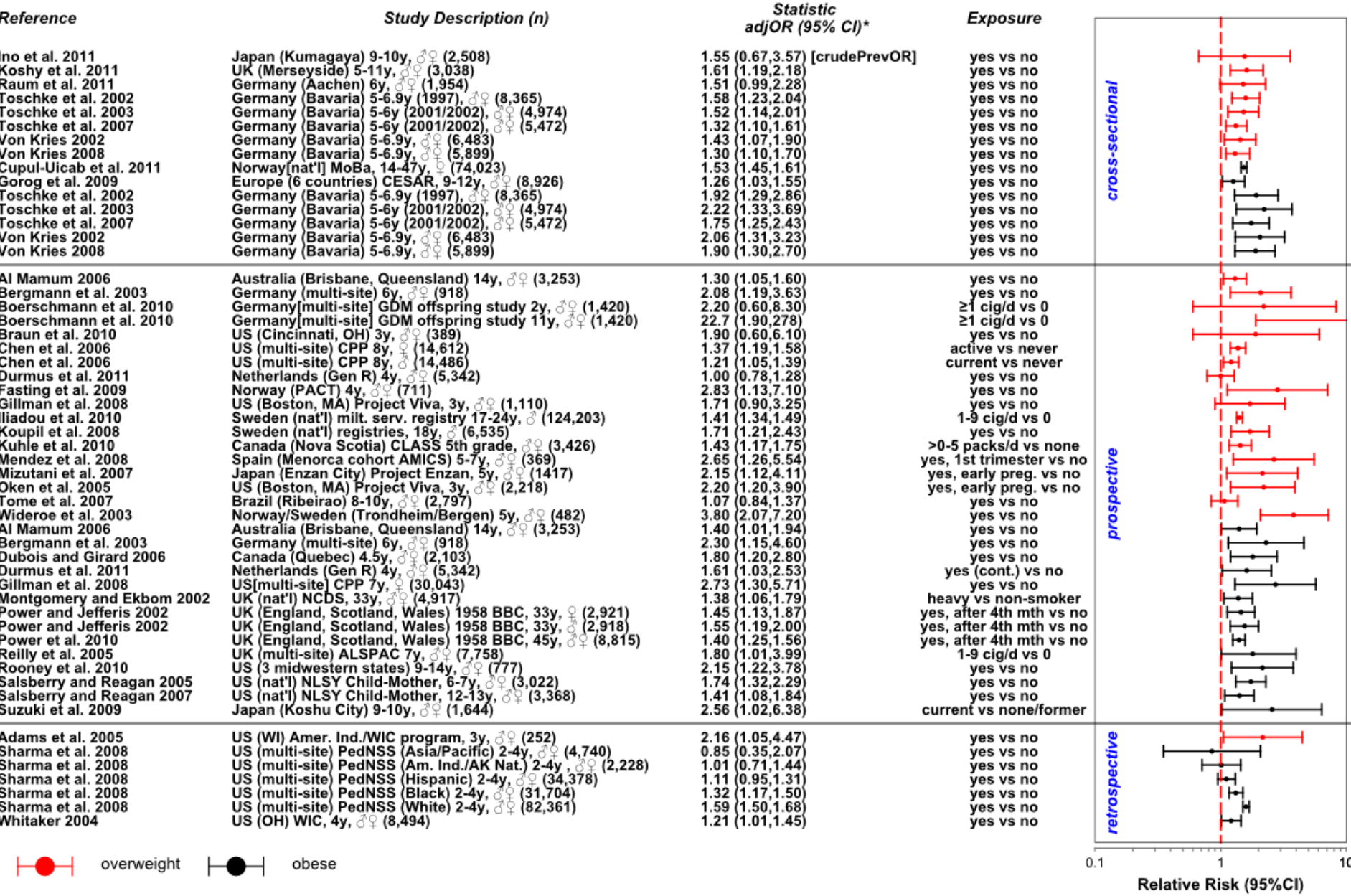


Figure 2. Human studies on exposure to smoking during pregnancy and findings related to T1D

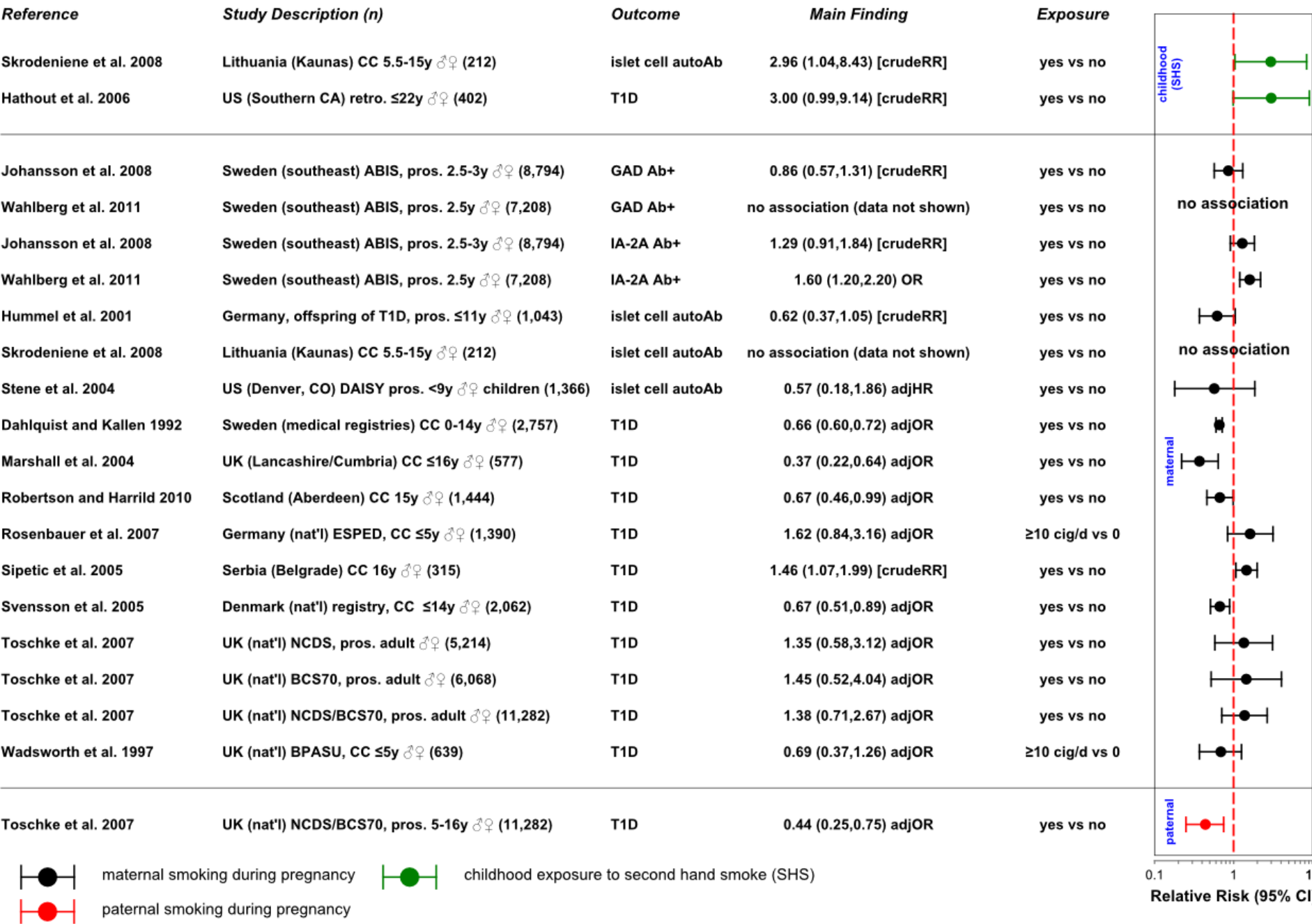


Figure 3. Human studies on exposure to smoking during pregnancy and findings related to T2D or metabolic syndrome

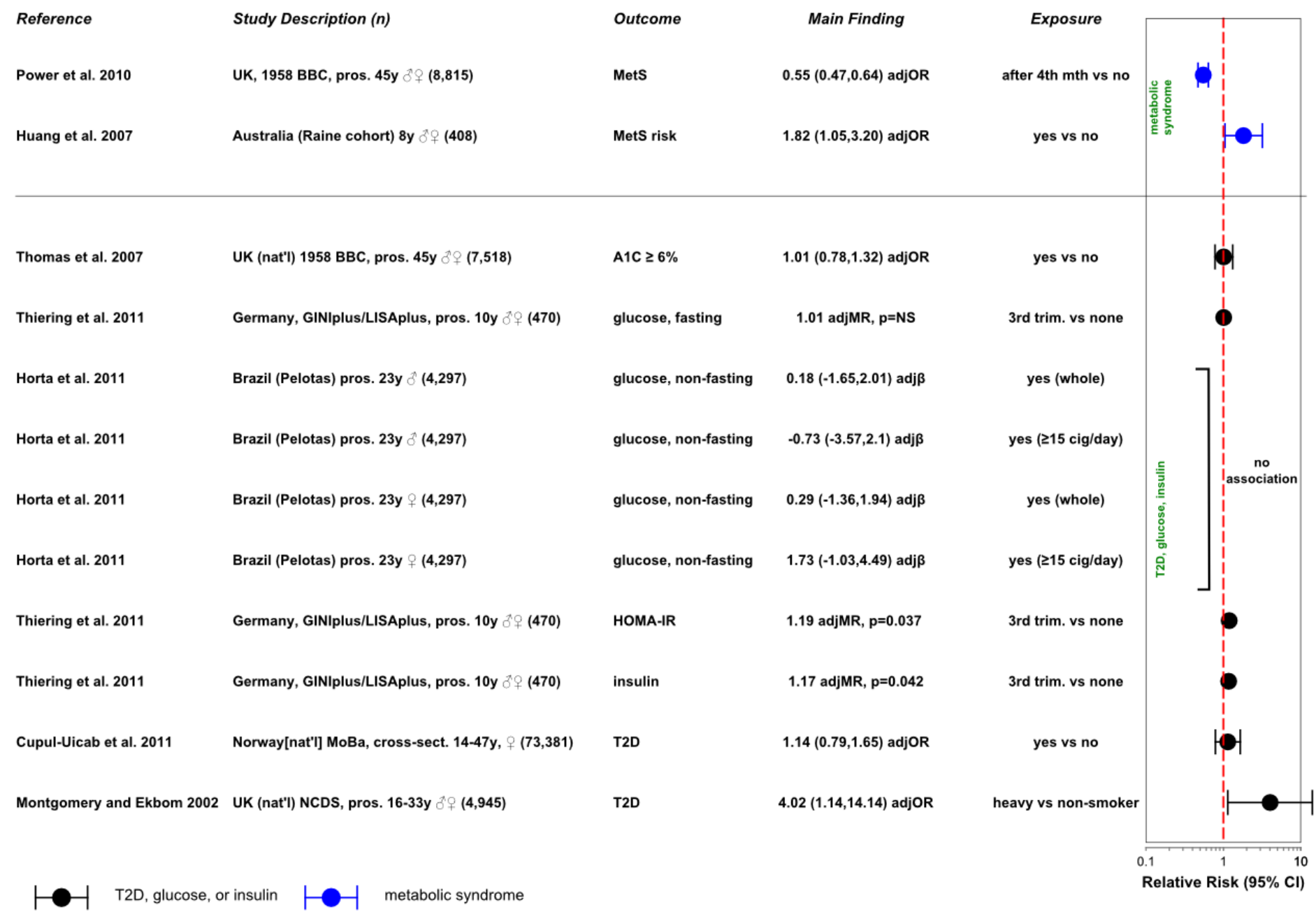
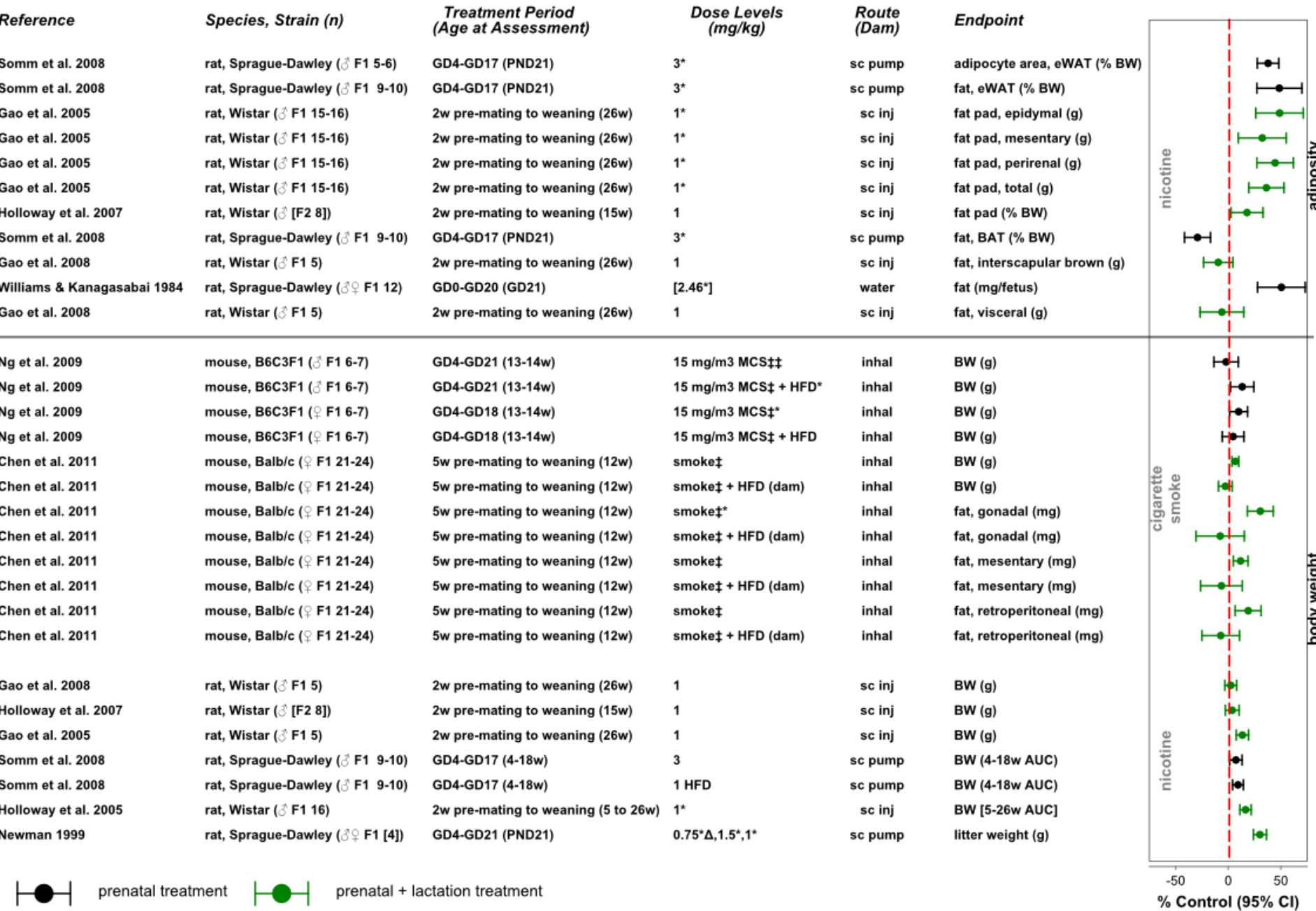


Figure 4. Animal studies of prenatal or prenatal to lactational exposure to nicotine or cigarette smoking and adiposity-related endpoints



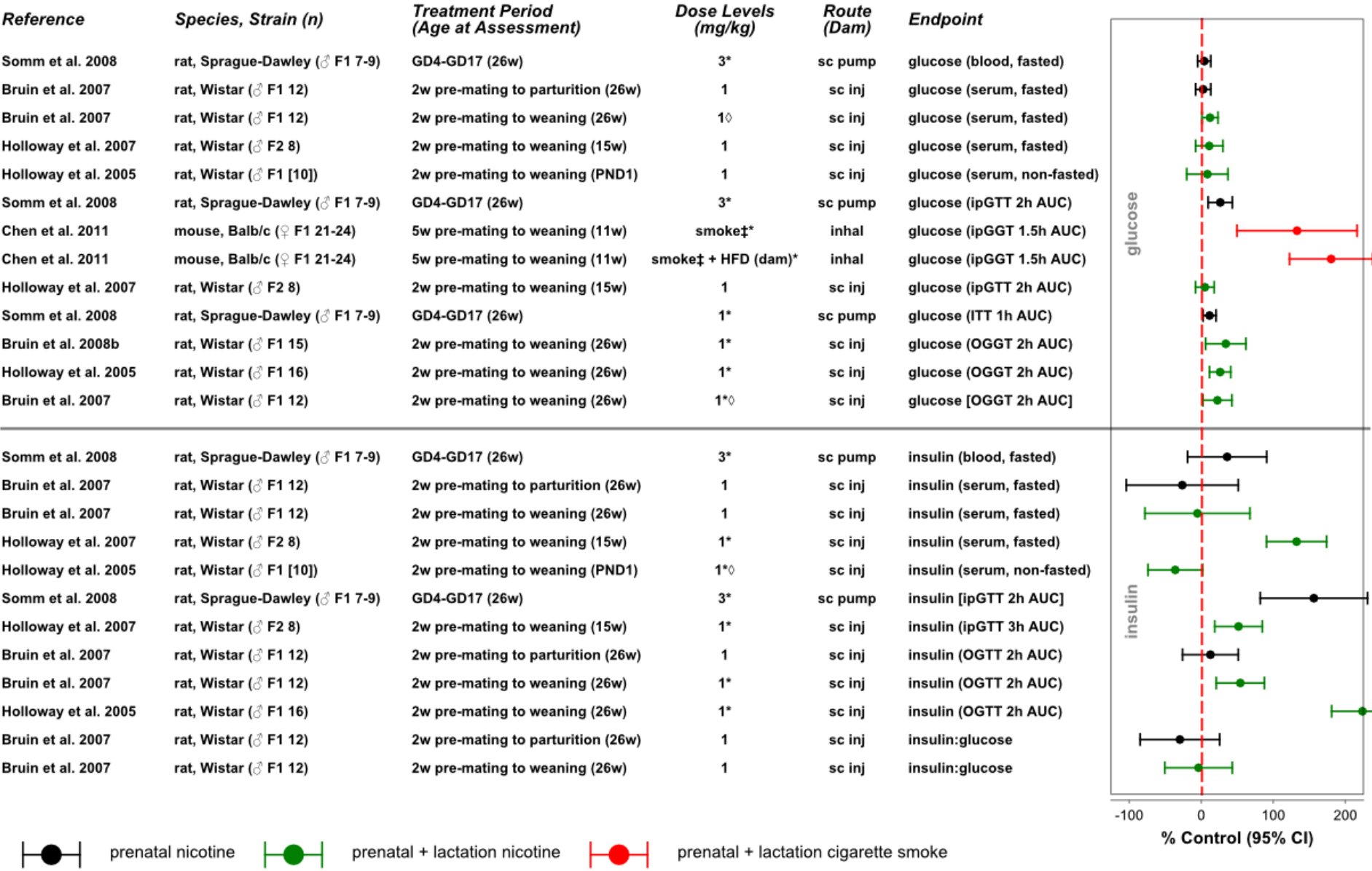


Figure 6. Animal studies of prenatal or prenatal to lactational exposure to nicotine and pancreatic endpoints

